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(54) Title: A LIQUID PHARMACEUTICAL FORMULATION COMPRISING NICOTINE FOR THE ADMINISTRATION TO THE ORAL CAVITY

(57) Abstract: A liquid pharmaceutical formulation comprising nicotine in any form for administration to the oral cavity being alkalized by buffering and/or pH regulation. The administration is preferably by spraying and most preferably by spraying under the tongue. A method for manufacturing said formulation. Use of said formulation in therapy, such as therapy for treating addiction to tobacco.



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**A liquid pharmaceutical formulation comprising nicotine
for the administration to the oral cavity**

Technical Field

This invention relates to a liquid pharmaceutical formulation for delivering
5 nicotine to a subject. This invention also relates to a method and a system for delivering nicotine as well as manufacturing and use of said liquid pharmaceutical formulation.

Background of the Invention

Tobacco dependence and reduction thereof

10 In recent years, with the recognition of the harmful effects of tobacco smoking, there have been numerous campaigns and programs by governmental agencies and various health groups and other interested organisations to disseminate information about the adverse health effects resulting from tobacco smoking. Moreover, and as a result of this recognition of the harmful effects, there have been many
15 programs directed to attempts in reducing smoking incidence.

Nicotine is an organic compound and is the principal alkaloid of tobacco. Nicotine is the chief active ingredient in the tobacco used in cigarettes, cigars, snuff and the like. Nicotine is also an addictive drug, though, and smokers characteristically display a strong tendency to relapse after having successfully stopped smoking
20 for a time. Nicotine is the world's second most used drug, after caffeine from coffee and tea.

The main problem with tobacco smoking is its enormous implications on health. Today it is estimated that smoking-related diseases cause some 3 – 4 million deaths per year. In the US Surgeon General's 1988 report on The Health Consequences of Smoking, it was estimated that in the US alone about 300.000 deaths are
25 caused each year by diseases related to cigarette smoking. In fact, excessive smoking is now recognized as one of the major health problems throughout the world. This grim consequence of tobacco smoking has urged many medical associations and health authorities to take very strong actions against the use of tobacco.

30 Even though tobacco smoking is decreasing in many developed countries today it is hard to see how the societies could get rid of the world's second most used drug.

The most advantageous thing a heavy smoker can do is to reduce or preferably even stop smoking completely. Experience shows, however, that most smokers find this extremely difficult since, mostly, tobacco smoking result in a dependence disorder or craving. The WHO has in its International Classification of Disorders a diagnosis called Tobacco Dependence. Others, like the American Psychiatric Association call the addiction Nicotine Dependence. It is generally accepted that these difficulties to stop smoking result from the fact that those heavy smokers are dependent on nicotine. The most important risk factors are, however, substances that are formed during the combustion of tobacco, such as carcinogenic tar products, carbon monoxide, aldehydes, and hydrocyanic acid.

Effects of nicotine

The administration of nicotine can give satisfaction and the usual method is by smoking, either by smoking e g a cigarette, a cigar or a pipe, or by snuffing or chewing tobacco. However, smoking has health hazards and it is therefore desirable to formulate an alternative manner of administering nicotine in a pleasurable manner that can be used to facilitate withdrawal from smoking and/or used as a replacement for smoking.

Upon smoking of a cigarette, nicotine is quickly absorbed into the smoker's blood and reaches the brain within around ten seconds after inhalation. The quick uptake of nicotine gives the consumer a rapid satisfaction, or kick. The satisfaction, then, lasts during the time of smoking the cigarette and for a period of time thereafter. The poisonous, toxic, carcinogenic, and addictive nature of smoking has provided efforts for methods, compositions and devices, which help in breaking the habit of smoking.

Nicotine is an addictive poisonous alkaloid $C_5H_4NC_4H_7NCH_3$, derived from the tobacco plant. Nicotine is also used as an insecticide. Approximately forty milligrams of nicotine may kill an adult (Merck Index).

Nicotine replacement products

One way to reduce smoking is to provide nicotine in a form or manner other than by smoking and some products have been developed to fulfill this need. Nicotine containing formulations are currently the dominating treatments for tobacco

dependence.

The success in achieving reduction in the incidence of smoking has been relatively poor using presently known products. State of the art involves both behavioral approaches and pharmacological approaches. More than 80% of the tobacco smokers who initially quit smoking after using some behavioral or pharmacological approach to singly reduce smoking incidence generally relapse and return to the habit of smoking at their former rate of smoking within about a one year's period of time.

As an aid for those who are willing to stop smoking there are several ways and forms of nicotine replacement products available on the market, such as nicotine chewing gums according to US 3,845,217. Several methods and means have been described for diminishing the desire of a subject to use tobacco, which comprises the step of administering to the subject nicotine or a derivative thereof as described in e g US 5,939,100 (nicotine containing microspheres) and US 4,967,773 (nicotine containing lozenge).

The effects of pH on the absorption of nicotine is discussed e g in Eur J Clin Pharmacol, Vol. 56, 2001, pages 813 – 818, L. Molander et al, "Pharmacokinetic investigation of a nicotine sublingual tablet". The effects of pH on a liquid nicotine formulation for administration to the oral cavity are though not disclosed.

The use of skin patches for transdermal administration of nicotine has been reported (Rose, in Pharmacological Treatment of Tobacco Dependence, (1986) pp. 158 - 166, Harvard Univ. Press). Nicotine-containing skin patches that are in wide use today can cause local irritation and the absorption of nicotine is slow and affected by cutaneous blood flow.

Nicotine-containing nose drops have been reported (Russell et al., British Medical Journal, Vol. 286, p. 683 (1983); Jarvis et al., British Journal of Addiction, Vol. 82, p. 983 (1987)). Nose drops, however, are difficult to administer and are not convenient for use at work or in other public situations. Ways of administering nicotine by way of delivery directly into the nasal cavity by spraying is known from US 4,579,858, DE 32 41 437 and WO/93 127 64. There may, though, be local nasal

irritation with use of nasal nicotine formulations. The difficulty in administration also results in unpredictability of the dose of nicotine administered.

Also, inhaling devices resembling a cigarette are known for uptake of nicotine vapors as suggested in US 5,167,242. An aerosol for depositing nicotine in the
5 lungs is disclosed in DE 32 41 437.

Mouth sprays comprising nicotine are known in the art, e g according to US 6,024,097 wherein is disclosed a method of assisting a smoker in giving up the smoking habit whereby is used a plurality of aerosol dispensers comprising progressively lesser concentrations of nicotine. The aerosol is intended to be administered into the mouth. The liquid in the dispensers essentially consists of nicotine
10 and alcohol.

A similar mouth spray is disclosed in US 5,810,018, whereby in addition the aerosol comprises progressively greater concentrations of at least one selected stimulant.

15 WO 98/24420 discloses an aerosol device with an active and a propellant. The device may be used for e g sublingual administration. Nicotine is mentioned as an active in a long "laundry list" of drugs. There are though no examples on nicotine formulations.

US 5,721,257 discloses a method for treating a condition responsive to nicotine therapy comprising a first treatment with transdermally administered nicotine
20 and a second treatment with transmucosally administered nicotine. It is stated that the transmucosal administration may be accomplished via an aerosol to the nasal membranes. No administration to the oral cavity is disclosed.

WO 97/38663 discloses a buccal aerosol spray using a non-polar solvent.
25 Nicotine is mentioned as one useful active in this spray.

US 5,955,098 likewise discloses a buccal non-polar spray wherein nicotine may be an active.

None of the known mouth sprays comprise any buffering and/or pH regulating means.

Prior art and problems thereof

The captioned means and methods do not satisfy the craving that certain users of tobacco experience. Specifically these means and methods generally do not provide for a sufficiently rapid uptake of nicotine without adverse effects.

5 This means that none of the hitherto known means and methods satisfactorily fulfills the following well-known NRT teaching by Russel et al:

I: A fast delivery or "boost" of nicotine, sufficiently rapid to give positive subjective nicotine effects in contrast with current nicotine gums and patches, will lead to faster craving relief, and

10 II: faster craving relief will give better craving control, and

III: better craving control should result in higher overall quit rates.

For the captioned see Russel, M.A.H., Stapleton, J.A. and Feyerabend C.

Nicotine boost per cigarette as the controlling factor of intake regulation of smokers; In: Clark et al. (Eds.) Effects of Nicotine on Biological Systems II,

15 Advances in Pharmacological Sciences, Birkhäuser Verlag, Basel, (1995) 233-238.

In light of the aforementioned problems there is a strong need and interest to develop means and methods for the administration of nicotine to provide a fast satisfaction to a person craving for nicotine or to provide a sense of smoking satisfaction without smoking, whereby also may be avoided problems associated
20 with the prior art means and methods. The present invention addresses said need and interest.

Summary of the Invention

In view of the foregoing disadvantages known in the art when trying to deliver nicotine to a subject so as to obtain a rapid transmucosal uptake of nicotine
25 in the oral cavity of the subject the present invention provides a new and improved product, systems and methods for obtaining a rapid transmucosal uptake of nicotine in the oral cavity of the subject.

Objects of the present invention are to provide an efficient and effective product, as well as methods and systems for a rapid uptake of nicotine in a subject
30 to avoid the disadvantages of previously known products and methods. The present invention also satisfactorily satisfies the above teaching of Russel et al.

Thus, the present invention provides a method for delivering nicotine in any form to a subject comprising administering to a subject a liquid pharmaceutical formulation containing nicotine in any form into the oral cavity of the subject and allowing the nicotine in any form to be absorbed into the systemic circulation of the subject essentially by rapid buccal uptake of nicotine as well as a method for manufacturing said liquid pharmaceutical formulation.

The present invention also provides a method for obtaining reduction of the urge to smoke or use tobacco containing material and/or for providing a fast sense of smoking satisfaction without smoking, comprising the steps of replacing at least partly the tobacco containing material with said liquid pharmaceutical formulation, administering to a subject a liquid pharmaceutical formulation containing nicotine in any form into the oral cavity of the subject and allowing the nicotine to be systemically absorbed by the subject essentially by buccal uptake of nicotine.

Furthermore, the present invention provides a system for delivering nicotine in any form to a subject, comprising said liquid pharmaceutical formulation and at least one other means for obtaining reduction of the urge to smoke or use of tobacco as well as a system for obtaining reduction of the urge to smoke or otherwise use of tobacco and/or for providing a sense of smoking satisfaction without smoking, comprising a liquid pharmaceutical formulation as per above and at least one other method for obtaining reduction of the urge to smoke or otherwise use tobacco. Said system may be a system wherein the at least one other method is selected from the group consisting of administration through chewing gums, nasal sprays, transdermal patches, inhaling devices, lozenges, tablets and parenteral methods, subcutaneous methods, intravenous methods, rectal methods, vaginal methods and transmucosal methods; or other use of tobacco.

The present invention provides for a flexible, convenient and discrete use in comparison with other means for transmucosal delivery of nicotine, e.g. chewing gums, lozenges and tablets. No chewing or sucking is necessary. Further and in contrast to other transmucosal dosage forms the present liquid pharmaceutical formulation provides nicotine in a form being directly buccally absorbable by a subject. Known formulations for nasal delivery of nicotine are inconvenient – side

effects include running nose, nasal irritation and irritation of the eyes. The nicotine in chewing gums, lozenges and tablets need pass a transformation phase, involving e.g. mastication, disintegration, melting and/or dissolution, prior to being present in a directly absorbable form. A nicotine patch provides for a discrete administration, but does not provide for a fast uptake of nicotine.

A product according to the present invention is alkalized by buffering and/or pH regulation in such a way that upon administration of the liquid pharmaceutical formulation the pH of the liquid of the oral cavity is increased by 0.3 - 4 pH units, or preferably increased by 0.5 - 2.5 pH units.

Use of said product will according to the invention rapidly deliver nicotine in any form to a subject and will also provide for obtaining a quick and/or sustained and/or complete reduction of the urge to smoke or use tobacco and/or for providing a sense of smoking satisfaction without smoking resembling the sense of smoking satisfaction obtained after regular smoking or use of tobacco.

Legend of Figures

Figure 1 is a diagram showing venous blood plasma level concentrations of nicotine after two different ways of administering nicotine. For both ways of administration one unit dose was administered at time zero. No further doses were administered. 50 persons, all being nicotine users, took part in this test. "Spray" represents 200 µl of a liquid pharmaceutical formulation according to below Example 4 being sprayed under the tongue. This unit dose comprised 3.5 mg nicotine measured as free base. "Microtab" represents one tablet of Nicorette® Microtab, comprising 4 mg nicotine measured as free base. Nicorette® Microtab is pharmacologically equivalent to Nicorette® Gum. "Spray" comprises a buffer. "Microtab" comprises no buffer. With "Spray" the liquid pharmaceutical formulation was held in the mouth for one minute before swallowing. With "Microtab" the tablet was kept under the tongue until dissolved. Each symbol on the respective graph represents one measurement of nicotine in venous blood plasma.

Figure 2 shows mean plasma concentrations after sublingual administration of three liquid pharmaceutical formulations with pH 6, 7 and 8.5 respectively. For each formulation 200 µl was sprayed under the tongue at time zero. For all said

three formulations the concentration of nicotine was 10 mg/ml, i.e. each 200 µl spray dose as above contained 2 mg nicotine calculated as free base. The formulation with pH 8.5 was a formulation according to below Example 1. The formulations with pH 7 and pH 6 were formulations according to below Example 2 and Example 3 respectively.

Figure 3 compares the venous blood nicotine plasma profile vs. time of a single dose of the current Nicorette® Gum, extra strength (4 mg), with the corresponding plasma profile when smoking a "light" (low-nicotine) cigarette. One objective with the present invention is to obtain a buccal nicotine formulation providing for a pK profile being closer to the pK profile for a cigarette than is provided using presently known buccal nicotine formulations.

Figure 4 shows the mean score values from 52 smoking volunteers in a randomized open study of the "urge to smoke" (craving), as estimated and recorded on a visual analogue scale (VAS) as a function of time when the same formulations as in Fig. 1 were used. The craving scores were recorded directly after smoking one cigarette and during the abstinence of 7 hours before the administration of the nicotine products. The scores were then recorded more frequently during 1 hour after the administration. The heart rate was also monitored in this study. This figure clearly shows that the present invention provides for a much faster reduction of the urge to smoke score than do present buccal nicotine formulations. For example, about 2 minutes after administration of a formulation according to the present invention the craving score is reduced by 50 %. With Nicorette® Microtab a 50 % decrease in craving score is obtained only more than 10 minutes after administration.

Detailed Description of the Invention

Definitions

The terms "tobacco", "tobacco containing material" and similar are herein intended to mean such material for any type of use of tobacco including smoking, snuffing or chewing whereby is used inter alia a cigarette, a cigar, pipe tobacco, snuff and chewing tobacco.

The term "fast reduction of the urge to smoke or use tobacco " is herein intended to mean an initial priming of the subject so as to achieve a reduction of the urge to smoke or use tobacco.

The term "transient" is intended to pertain to a non-permanent change of a
5 biological and/or physiological state, upon which after a certain period of time said state will return to its value or behavior prior to said change.

The term "buccal" and "buccally" are herein intended to pertain to all of or any part of the soft tissue lining of the oral cavity.

The term "liquid of the oral cavity" is herein intended to mean saliva and/or
10 saliva mixed with a quantity of the liquid pharmaceutical formulation.

The term "incidence of administration" is herein intended to mean administration of one or more single doses of the liquid pharmaceutical formulation within the same time frame, said time frame being dependent on the needs of the subject receiving the administration, said time frame extending from a few seconds to
15 around ten minutes.

The buffering agent and the pH regulating means

Absorption of nicotine from the oral cavity to the systemic circulation is dependent on the pH of the saliva and the pKa of nicotine, which is about 7.8. Assuming a pH of the saliva of 6.8 only about 10% of the nicotine in saliva will be in the
20 free base form. Thus, in order to promote absorption of nicotine in a free base form, which is the form predominantly absorbed through the mucosa, the pH of the saliva must be increased. At a pH of 8.8 about 90% of the nicotine in saliva will then be in the free base form.

Hence and according to the invention, the liquid pharmaceutical formulation
25 is alkalized by buffering and/or pH regulation. This may be achieved by including physiologically acceptable buffering substances or agents, or by other means. With other means it is intended to include buffering by any component in the product, which may not normally act as a buffering agent, such as a self-buffering additive and/or pH regulating forms of nicotine.

30 By buffering and/or pH regulation thereby increasing the pH of the saliva the uptake of nicotine is changed, e.g. increased compared to the nicotine uptake when

the saliva is not alkalized by buffering and/or pH regulation. Also, since the trans-mucosal uptake of nicotine in the oral cavity according to the invention is faster than for nicotine not being buffered and/or pH regulated according to the invention, less nicotine will be swallowed and reach the gastrointestinal (GI) tract. The nicotine that reaches the GI tract will be subjected to first pass metabolism, which reduces the total amount of intact nicotine absorbed additionally reducing the rate of nicotine absorption. This means that the absorption kinetics of nicotine that is not co-administered with a buffer according to the invention will generally be slower and the bioavailability will generally be lower than when administered together with a buffer.

For buffering may be used one or more buffering agents selected from the group consisting of carbonates including bicarbonate or sesquicarbonate, glycinate, phosphate, glycerophosphate or citrate of an alkali metal, such as potassium or sodium, or ammonium, and mixtures thereof.

Further embodiments may use trisodium or tripotassium citrate, and mixtures thereof.

Still further embodiments may comprise different phosphate systems, such as trisodium phosphate, disodium hydrogen phosphate; and tripotassium phosphate, dipotassium hydrogen phosphate, and calcium hydroxide, sodium glycinate; and mixtures thereof.

Alkali metal carbonates, glycinate and phosphates are preferred buffering agents.

The pH regulation may also be obtained by using pH-regulating forms of nicotine, e g nicotine free base.

The amount of the buffering agent or agents in the liquid pharmaceutical formulation is preferably sufficient in the specific embodiments to raise the pH of the saliva to above 7, as specified above and, to maintain the pH of the saliva in the oral cavity above 7, e g pH 7 - 11. Otherwise expressed the liquid pharmaceutical formulation should be alkalized by buffering and/or pH regulation in such a way that upon administration to a subject the pH of the liquid of the oral cavity of the subject is transiently increased by about 0.3 - 4 pH units, preferably by about 0.5 -

2.5 pH units. The amount of buffering agent(s) required to achieve such an increase in pH is readily calculated by a person skilled in the art.

The nicotine may be formulated in different forms, e g in different complexes or salts or as free base.

5 The active ingredient

According to the invention, the liquid pharmaceutical formulation product comprises nicotine in any form to provide a fast transmucosal uptake of the nicotine in the oral cavity of a subject so as to obtain a reduction of the urge to smoke and/or use tobacco, and/or a rapid "nicotine kick" and/or a "nicotine head rush". Thereby
10 may also be achieved a systemic maintenance level of nicotine.

The nicotine should be in a saliva soluble form to facilitate the subsequent uptake of the nicotine from the saliva in the oral cavity into the systemic circulation of the subject.

In preferred embodiments, the nicotine in any form is primarily selected from
15 the group consisting of the free base form of nicotine, a nicotine salt, a nicotine derivative, a nicotine inclusion complex or nicotine in any non-covalent binding; and mixtures thereof.

Still further the inclusion complex may be a cyclodextrin, such as β -cyclodextrin.

20 Even more further the nicotine salt may be a tartrate, hydrogen tartrate, citrate or malate.

According to the invention, the uptake of the nicotine through any tissue or mucosa in the oral cavity is improved in relation to the uptake obtained by a liquid nicotine-containing pharmaceutical formulation devoid of alkalizing buffering
25 agents or devoid of alkalizing pH-regulating means.

The nicotine may act as a stimulant to e g obtain a rapid reduction of the urge to smoke or to use tobacco.

With nicotine it is intended to include nicotine, 3-(1-methyl-2-pyrrolidinyl)-pyridine, with its base form, including synthetic nicotine as well as nicotine extracts
30 from tobacco plants, or parts thereof, such as the genus *Nicotiana* alone or in combination; or pharmaceutically acceptable salts.

The most preferable embodiment incorporates nicotine as the free base form or as a water-soluble pharmaceutically acceptable salt, or as an inclusion complex, such as a cyclodextrin complex, e g β -cyclodextrin. But any other suitable pharmaceutically acceptable form may also be employed.

- 5 Numerous nicotine salts are known, and may be used, e g the salts presented in Table 1, such as preferably the tartrate, hydrogen tartrate, citrate, malate, and/or hydrochloride.

Table 1 Possible acids used for nicotine salt formation

Acid	Molar ratio* of Acid:nicotine
Formic	2:1
Acetic	3:1
Propionic	3:1
Butyric	3:1
2-Methylbutyric	3:1
3-Methylbutyric	3:1
Valeric	3:1
Lauric	3:1
Palmitic	3:1
Tartaric	2:1
Citric	2:1
Malic	2:1
Oxalic	2:1
Benzoic	1:1
Gentisic	1:1
Gallic	1:1
Phenylacetic	3:1
Salicylic	1:1
Phthalic	1:1
Picric	2:1
Sulfosalicylic	1:1
Tannic	1:5
Pectic	1:3
Alginic	1:2
Hydrochloric	2:1
Chloroplatinic	1:1
Silicotungstic	1:1
Pyruvic	2:1
Glutamic	1:1
Aspartic	1:1

* recommended upon manufacturing

Amount of the nicotine in the liquid pharmaceutical formulation

- 5 The nicotine in any form is according to the invention formulated to provide the subject with a dose to achieve an effect. The effect may be to provide a sense of

smoking satisfaction without smoking. Another effect of the administered nicotine in any form may be a reduction of the urge to smoke or use tobacco.

The effect may also be a combination of a reduction of said urge and providing a sense of smoking satisfaction without smoking. The amount of the nicotine
5 should be sufficient to provide such an effect in a subject. This amount may, of course, vary from person to person.

According to the invention, embodiments of the liquid pharmaceutical formulation comprise nicotine in such concentrations that the amount of nicotine delivered at each incidence of administration is about 0.05 - 10 mg calculated as the
10 free base form of nicotine, preferably about 0.25 - 6 mg and most preferably about 0.5 - 4 mg.

Release and uptake of nicotine

Presently existing pharmaceutical administration forms for oral administration of nicotine normally provide a slow release and a slow uptake of the nicotine
15 compared to smoking. The slow uptake of the nicotine provides a t_{\max} , i.e. the time-point where the nicotine has its maximum level measured in the plasma of venous blood after a single dose at about 30 - 45 minutes after administration.

The time point for reaching a sense of satisfaction or reduction of urge to smoke or use tobacco after administration is individual, but may in existing pharmaceutical forms for administering nicotine generally be reached after approximately
20 30 minutes when regarded as coinciding with t_{\max} . According to the present invention, such a sense of satisfaction may be reached after a shorter period of time due to a rapid transmucosal uptake in the oral cavity due to the buffering and/or pH regulation and due to the absence of rate-limiting steps, such as tablet or lozenge
25 melting, tablet or lozenge disintegration and dissolution and chewing gum mastication, followed by drug dissolution.

The liquid phase

The liquid phase of the present liquid pharmaceutical formulation may comprise water. The liquid phase may also comprise an alcohol, such as ethanol,
30 glycerol, propylene glycol and polyethylene glycol, or mixtures thereof. It may also

comprise one or more lipids. Further it may comprise mixtures of the above ingredients.

Other additives to the liquid pharmaceutical formulation

Other additives may be added optionally to the liquid pharmaceutical formulation.

Optional additives comprise one or more stabilizing additives, such as those selected from the group consisting of antioxidants including vitamin E, i.e. tocopheroles, vitamin C, i.e. ascorbic acid and its salts, sodium pyrosulfite, butylhydroxytoluene, butylated hydroxyanisole; and preservatives including parabenes, benzalkonium chloride, chlorbutanol, benzyl alcohol, beta-phenylethyl alcohol, cetylpyridinium chloride; and chelating agents, such as EDTA; and galates, such as propyl galate.

Further optional additives comprise one or more additives selected from the group consisting of:

- enhancers, such as azone;
- vitamins, such as vitamins C and E;
- minerals, such as fluorides, especially sodium fluoride, sodium monofluorophosphate and stannous fluoride;
- anti-odours, such as zinc and cyclodextrins;
- propellants, such as 1,1,2,2-tetrafluoroethane (HFC-134a), optionally being liquefied, and 1,1,1,2,3,3,3-heptafluoropropane (HFC-227), optionally being liquefied;
- sweeteners including one or more synthetic sweetening agents and/or natural sugars, such as those selected from the groups consisting of artificial sweeteners e.g. saccharin and its sodium and calcium salts, aspartame, acesulfame and its potassium salt, thaumatin and glycyrrhizin;
- polyhydric alcohols such as sorbitol, xylitol, mannitol and glycerol;
- monosaccharides including glucose (also called dextrose), fructose (also called laevulose) and galactose;
- disaccharides including saccharose (also called sucrose), lactose (also called milk sugar) and maltose (also called malt sugar);

- mixtures of sugars including liquid glucose syrup e g starch hydrolysates containing a mixture of chiefly dextrose, maltose, dextrans and water, invert sugar syrup e g sucrose inverted by invertase containing a mixture of dextrose, laevulose and water, high sugar content syrups such as treacle, honey and malt extract;
5 and mixtures thereof;
- flavoring and/or aromatizing agents, such as those selected from the group consisting of essential oils obtained by distillations, solvent extractions or cold expressions of fresh or dried flowers, buds, leaves, stems, fruit, seeds, peel, bark, or root e g oil of peppermint, spearmint, eucalyptus, wintergreen, niaouli,
10 clove, cardamom, cinnamon, bitter almond, coriander, caraway, ginger, juniper, orange, bitter orange, lemon, grapefruit, mandarine, bergamot, thyme, fennel and rosemary;
- natural flavors and aroma agents including either diluted solutions of essential oils or concentrates of flavor components with natural origin from e g fruits,
15 berries, nuts, spices, mints, tobacco, cocoa, coffee, tea, vanilla, liquorice, caramel, toffee, honey, wine, liquors and brews;
- synthetic flavors and aroma agents consisting of mixtures of chemicals comprising hydrocarbons, alcohols, aldehydes, esters, ketones, ethers and oxides blended to match the natural flavor of e g fruits, berries, nuts, spices, mints,
20 tobacco, cocoa, coffee, tea, vanilla, liquorice, caramel, toffee, honey, wine, liquors or brews;
- and mixtures thereof.

Surface active agents

One or more of the compounds of the liquid pharmaceutical formulation may
25 be solubilized in one or more surface active agents and/or emulsifiers, such as nonionic, cationic, anionic or zwitterionic surfactants, including amphiphilic block copolymers, or mixtures thereof.

Specifically one or more of the compounds of the liquid pharmaceutical formulation may be solubilized in one or more surface-active agents selected from
30 nonionic surface-active agents including poloxamers, e g:

- poly (oxypropylene)-poly (oxyethylene) block copolymers, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, mono- and diglycerides and esters thereof, polyoxyethylene stearates, polyglycerolesters of fatty acids (including polyglycerolpolyricinoleic acid (PGPR)), and sorbitan fatty acid esters,
- cationic surface-active agents including secondary, quaternary and tertiary ammonium compounds and cationic phospholipids,
- anionic surface-active agents including fatty acid salts, lactylates, especially sodium and/or calcium stearylactylate, alkyl sulphates, alkyl sulphonates, latanol,
- and anionic phospholipids, such as phosphatidylserine,
- zwitterionic surface-active agents including zwitterionic phospholipids, such as phosphatidylcholine and phosphatidylethanolamine,
- or mixtures thereof,
- preferably surface-active agents or mixtures thereof being nonionic.

15 Method for delivering nicotine in any form to a subject

According to the invention, a method for delivering nicotine in any form to a subject comprises the steps of:

- a) administering to a subject a liquid pharmaceutical formulation product containing nicotine in any form according to the invention into the oral cavity of the subject, and
- b) allowing the nicotine in any form in the liquid pharmaceutical formulation to be mixed with the saliva in the oral cavity and absorbed into the blood plasma of the subject essentially by buccal uptake.

One embodiment results in a t_{\max} of nicotine in venous blood of the subject after about 3 - 30 minutes.

One further embodiment results in a t_{\max} of nicotine in venous blood of the subject after about 3 - 20 minutes.

In still one further embodiment, said nicotine in any form is absorbed resulting in a t_{\max} of nicotine in venous blood of the subject after about 3 - 15 minutes.

30 Method for obtaining reduction of the urge to smoke or use tobacco

A method for obtaining reduction of the urge to smoke or use tobacco-con-

taining material and/or for providing a sense of smoking satisfaction without smoking according to the invention comprises the steps of:

- a) replacing at least partly the tobacco containing material with a liquid pharmaceutical formulation according to any of claims 1 - 22,
- 5 b) administering to a subject a liquid pharmaceutical formulation containing nicotine in any form according to any of claims 1 - 22 into the oral cavity of the subject, and
- c) allowing the nicotine in any form in the liquid pharmaceutical formulation to be absorbed by the subject essentially by buccal uptake.

10 The administration to the oral cavity takes place by spraying, dropping or pipetting, preferably by spraying, most preferably by spraying under the tongue. The administration is intended for the oral cavity, not for e g the lungs or the upper respiratory tract.

In one embodiment said nicotine in any form results in a t_{\max} of nicotine in
15 venous blood of the subject after about 3 - 30 minutes.

In one further embodiment said nicotine in any form results in a t_{\max} of nicotine in venous blood of the subject after about 3 - 20 minutes.

In still one further embodiment said nicotine in any form results in a t_{\max} of nicotine in venous blood of the subject after about 3 - 15 minutes.

20 Even further embodiments of the method for delivering nicotine to a subject may comprise the steps of combining at least one other method for obtaining reduction of the urge to smoke or use of tobacco.

The liquid pharmaceutical formulation may be used for obtaining a quick and/or sustained and/or complete reduction of the urge to smoke or use tobacco
25 and/or for providing a sense of smoking satisfaction without smoking as further discussed below.

The fast relief provides the subject with a sense of rapid smoking satisfaction without smoking.

One embodiment reduces the urge to smoke or use of tobacco by reaching a
30 t_{\max} of nicotine in venous blood of the subject after about 3 - 30 minutes by the use of a liquid pharmaceutical formulation according to the invention.

One further embodiment reduces the urge to smoke or use tobacco by reaching a t_{\max} of nicotine in venous blood of the subject after about 3 - 20 minutes by the use of a liquid pharmaceutical formulation according to the invention.

Still one further embodiment reduces the urge to smoke or use tobacco by reaching a t_{\max} of nicotine in venous blood of the subject after about 3 - 15 minutes by the use of a liquid pharmaceutical formulation according to the invention.

Cessation of the urge to smoke or use tobacco

For some of the users, it may be a goal to terminate the usage of nicotine completely, due to several reasons e g health, economical, social or behavioral. This may be achieved by further decreasing the delivered amount of nicotine in any form gradually over time. In specific embodiments of the invention, the method described above for obtaining craving relief may further comprise the steps of decreasing the amount of nicotine in the liquid pharmaceutical formulation gradually over time, and/or the steps of reducing the incidence of administration of the liquid pharmaceutical formulation gradually over time, and/or the steps of reducing the dosage size of the liquid pharmaceutical formulation gradually over time, so as to achieve a relief of tobacco craving and/or to achieve a sense of smoking satisfaction. This method results in a weaning process gradually over time.

Different types of smokers reach the sense of reduced craving at different plasma levels of nicotine. This may, of course, affect the individual types of programs for administering a liquid pharmaceutical formulation according to the invention. Different types of smokers include e g peak seekers or smokers that crave for a plasma level of nicotine constantly being above the level below which withdrawal symptoms occur.

One strategy may be to lower the frequency of administering the liquid pharmaceutical formulation. Other embodiments include varying the dose of the nicotine in said liquid pharmaceutical formulation as well as the combination of these two embodiments.

Systems for delivering nicotine and for obtaining craving relief

According to the invention there is a system for delivering nicotine in any form to a subject. Such a system comprises a liquid pharmaceutical formulation

according to the invention and at least one other means for obtaining reduction of the urge to smoke.

Another system according to the invention may be a system for obtaining reduction of the urge to smoke or use tobacco and/or for providing a sense of smoking satisfaction without smoking. Such a system comprises a liquid pharmaceutical formulation according to the invention and at least one other method for obtaining reduction of the urge to smoke or use tobacco. Other methods may be a concomitant or concurrent method selected from the group consisting of administration through chewing gums, nasal sprays, transdermal patches, inhaling devices, lozenges, tablets and parenteral methods, subcutaneous methods, intravenous methods, rectal methods, vaginal methods and transmucosal methods; or use of tobacco.

In a specific embodiment, the at least one other method comprises administration of nicotine.

Use of the liquid pharmaceutical formulation

The use of the liquid pharmaceutical formulation according to the invention is for obtaining a fast and/or complete reduction of the urge to smoke and use tobacco or for providing a sense of smoking without smoking as described above.

The dose of the nicotine is chosen to give the subject an individual sensory perception and satisfaction with an effect of the nicotine in any form. The use of the liquid pharmaceutical formulation may also be a sole use according to the invention or a combination with other means or methods known in the field of drug abuse. Specifically, the present invention may be used in combination with other means as described above in the methods in the paragraphs above.

The use may give a quick reduction of the urge to smoke or use tobacco whereby is reached a t_{\max} of nicotine in venous blood after about 3 - 20 minutes.

In a specific embodiment, the use of the liquid pharmaceutical formulation according to the invention will reduce the urge to smoke or use tobacco by reaching a t_{\max} of nicotine in venous blood of the subject after about 3 - 15 minutes.

According to the invention, a use of a liquid pharmaceutical formulation according to the invention is for delivering nicotine in any form to a subject.

In one embodiment, the delivering of nicotine in any form results in a t_{\max} of nicotine in venous blood of the subject after about 3 - 30 minutes.

In another embodiment, the delivering of nicotine in any form results in a t_{\max} of nicotine in venous blood of the subject after about 3 - 20 minutes.

5 In still another embodiment, the delivering of nicotine in any form results in a t_{\max} of nicotine in venous blood of the subject after about 3 - 15 minutes.

As readily shown and concluded from the figures, e g Figure 4, the shorter the t_{\max} the faster the relief of the craving, i e of the urge to smoke.

Examples on embodiments and manufacturing of the liquid

10 **pharmaceutical formulation**

The below examples are non-limiting and for illustrating the present invention. Alternatives and variations of the below examples within the scope of the present invention as per the below claims may be carried out by a person skilled in the art. Ingredients as per the below examples may be exchanged for equivalent
15 ingredients, preferably as per above. The formulations according to Examples 2 and 3 were made for comparative purposes as seen from Figure 2.

Example 1

Manufacturing of a 1000 ml formulation with 10 mg nicotine/ml and around pH 8.5.

20 **Mixture 1**

To a beaker containing 800 ml water of 90°C was added 0.7 g methyl parahydroxybenzoate, acting as preservative, and 0.3 g propyl parahydroxybenzoate, acting as preservative. The additives were dissolved during stirring for about 10 minutes. Then was added 10.45 g sodium dihydrogen phosphate, acting as buffering
25 agent, and 0.5 g EDTA, acting as chelating agent, to the solution, which was stirred for about 5 minutes. Then the solution was cooled to 30°C during stirring.

Mixture 2

To a beaker containing 15.9 g ethanol of room temperature, acting as solvent, was added 0.045 g peppermint oil, acting as flavoring agent. The liquid was mixed
30 for 2 minutes.

Final mixture

Mixture 2 was added during stirring to a beaker containing 150 ml water. Gently 10 g nicotine (base) was added to the beaker. Then Mixture 1 was added to the beaker and stirred for 5 minutes. The pH of the Final mixture was checked and
5 adjusted to about pH 8.5 with sodium hydroxide (20%) and to volume with water.

Example 2

Manufacturing of a 1000 ml formulation with 10 mg nicotine/ml and around pH 7.0.

This Example 2 differs from Example 1 only for pH. The formulation according to Example 2 contains a non-alkalizing buffering agent. This formulation was
10 for use as a comparison in Figure 2.

Mixture 1

To a beaker containing 800 ml water of 90°C was added 0.7 g methyl para-hydroxybenzoate, acting as preservative, and 0.3 g propyl para-hydroxybenzoate,
15 acting as preservative. The additives were dissolved during stirring for about 10 minutes. Then was added 10.45 g sodium dihydrogen phosphate, acting as buffering agent, and 0.5 g EDTA, acting as chelating agent, to the solution, which was stirred for about 5 minutes. Then the solution was cooled to 30°C during stirring.

Mixture 2

20 To a beaker containing 15.9 g ethanol of room temperature, acting as solvent, was added 0.045 g peppermint oil, acting as flavoring agent. The liquid was mixed for 2 minutes.

Final mixture

Mixture 2 was added during stirring to a beaker containing 150 ml water.
25 Gently 10 g nicotine (base) was added to the beaker. Then Mixture 1 was added to the beaker and stirred for 5 minutes. The pH of the Final mixture was checked and adjusted to about pH 7.0 with hydrochloric acid and to volume with water.

Example 3

Manufacturing of a 1000 ml formulation with 10 mg nicotine/ml and around
30 pH 6.0.

This Example 3 differs from Example 1 only for pH. The formulation according to Example 3 contains a non-alkalizing buffering agent. This formulation was for use as a comparison in Figure 2.

Mixture 1

5 To a beaker containing 800 ml water of 90°C was added 0.7 g methyl para-hydroxybenzoate, acting as preservative, and 0.3 g propyl para-hydroxybenzoate, acting as preservative. The additives were dissolved during stirring for about 10 minutes. Then was added 10.45 g sodium dihydrogen phosphate, acting as buffering agent, and 0.5 g EDTA, acting as chelating agent, to the solution, which was stirred
10 for about 5 minutes. Then the solution was cooled to 30°C during stirring.

Mixture 2

To a beaker containing 15.9 g ethanol of room temperature, acting as solvent, was added 0.045 g peppermint oil, acting as flavoring agent. The liquid was mixed for 2 minutes.

15 Final mixture

Mixture 2 was added during stirring to a beaker containing 150 ml water. Gently 10 g nicotine (base) was added to the beaker. Then Mixture 1 was added to the beaker and stirred for 5 minutes. The pH of the Final mixture was checked and adjusted to about pH 6.0 with hydrochloric acid and to volume with water.

20 Example 4

Manufacturing of a 1000 ml formulation with 17.5 mg nicotine/ml and around pH 9.0.

Mixture 1

To a beaker containing 600 ml water of room temperature was added 12.0 g
25 Synperonic® PE/F27, being a poloxamer acting as non-ionic surface active agent. The additive was dissolved during stirring for about 20 minutes. Then was added 0.5 g EDTA, acting as chelating agent, and 0.4 g sodium saccharin, acting as sweetener, to the liquid which was stirred until all ingredients were dissolved. Then was added 16.8 g sodium hydrogen carbonate, acting as buffering agent, and the
30 solution was stirred until a clear solution was obtained.

Mixture 2

To a beaker containing 250.0 g ethanol of room temperature, acting as solvent, was added 0.7 g methyl para-hydroxybenzoate acting as preservative, and 0.3 g propyl para-hydroxybenzoate acting as preservative. The liquid was mixed
5 until the ingredients were dissolved. Then was added 5.0 g peppermint oil, acting as flavoring agent, and 1.5 g aroma agent. The liquid was mixed until a clear solution was obtained.

Final mixture

Mixture 2 was gently added to Mixture 1 during stirring for about 1 minute.
10 Then was added 17.5 g nicotine (base) and the liquid was stirred for about 2 minutes. The pH of the Final mixture was checked and adjusted to around pH 9.0 with hydrochloric acid. The Final mixture was transferred to a 1000 ml volumetric flask and adjusted to 1000 ml volume by water. Finally the pH of the solution was checked to remain at around pH 9.0.

15 **Example 5**

Manufacturing of a 1000 ml formulation with 14.3 mg nicotine/ml and around pH 9.0.

Mixture 1

To a beaker containing 600 ml water of room temperature was added 20.0 g
20 Synperonic® PE/F27 being a poloxamer, acting as non-ionic surface active agent. The additive was dissolved during stirring for about 20 minutes. Then was added 2.0 g Acesulfame K, acting as sweetener, to the liquid which was stirred until all ingredients were dissolved. Then was added 20.0 g sodium hydrogen carbonate, acting as buffering agent, and the liquid was stirred until a clear solution was
25 obtained.

Mixture 2

To a beaker containing 95.0 g ethanol of room temperature, acting as solvent, was added 3.5 g peppermint oil, acting as flavoring agent, and 1.0 g aroma agent. The liquid was mixed until a clear solution was obtained.

Final mixture

Mixture 2 was gently added to Mixture 1 during stirring for about 1 minute. Then was added 14.3 g nicotine (base) and the liquid was stirred for about 2 minutes. The pH of the Final mixture was checked and adjusted to around pH 9.0 with hydrochloric acid. The Final mixture was transferred to a 1000 ml volumetric flask and adjusted to 1000 ml volume by water. Finally the pH of the solution was checked to remain at around pH 9.0.

The formulation according to Example 5 is a preferred composition.

Example 6

10 Manufacturing of a 1000 ml formulation with 14.3 mg nicotine/ml and around pH 9.0.

Mixture 1

To a beaker containing 600 ml water of room temperature was added 20.0 g Synperonic® PE/F27 being a poloxamer, acting as non-ionic surface active agent. 15 The additive was dissolved during stirring for about 20 minutes. Then was added 0.2 g benzalkonium chloride, acting as preservative, and 2.0 g Acesulfame K, acting as sweetener, to the liquid which was stirred until all ingredients were dissolved. Then was added 20.0 g sodium hydrogen carbonate, acting as buffering agent, and the liquid was stirred until a clear solution was obtained.

20 Mixture 2

To a beaker containing 95.0 g ethanol of room temperature, acting as solvent, was added 3.5 g peppermint oil, acting as flavoring agent, and 1.0 g aroma agent. The liquid was mixed until a clear solution was obtained.

Final mixture

25 Mixture 2 was gently added to Mixture 1 during stirring for about 1 minute. Then was added 14.3 g nicotine (base) and the liquid was stirred for about 2 minutes. The pH of the Final mixture was checked and adjusted to around pH 9.0 with hydrochloric acid. The Final mixture was transferred to a 1000 ml volumetric flask and adjusted to 1000 ml volume by water. Finally the pH of the solution was 30 checked to remain at around pH 9.0.

The formulation according to Example 6 is a another preferred composition.

Example 7

Manufacturing of a 1000 ml formulation with 14.3 mg nicotine/ml and around pH 9.0.

Mixture 1

- 5 To a beaker containing 600 ml water of room temperature was added 20.0 g Synperonic® PE/F27 being a poloxamer, acting as non-ionic surface active agent. The additive was dissolved during stirring for about 20 minutes. Then was added 0.5 g EDTA, acting as chelating agent, and 2.0 g Acesulfame K, acting as sweetener, to the liquid which was stirred until all ingredients were dissolved. Then
- 10 was added 20.0 g sodium hydrogen carbonate, acting as buffering agent, and the liquid was stirred until a clear solution was obtained.

Mixture 2

- To a beaker containing 95.0 g ethanol of room temperature, acting as solvent, was added 0.7 g methyl para-hydroxybenzoate acting as preservative, and 0.3 g
- 15 propyl para-hydroxybenzoate acting as preservative. The liquid was mixed until the ingredients were dissolved. Then was added 3.5 g peppermint oil, acting as flavoring agent, and 1.0 g aroma agent. The liquid was mixed until a clear solution was obtained.

Final mixture

- 20 Mixture 2 was gently added to Mixture 1 during stirring for about 1 minute. Then was added about 2 ml sodium hydroxide (50%) and 4 g nicotine bitartrate. The pH of the Final mixture was not allowed to decrease below pH 8 during the addition of the nicotine bitartrate. The preceding procedure with adding of sodium hydroxide and nicotine bitartrate was repeated until totally 40.7 g nicotine bitartrate
- 25 was added. The pH of the Final mixture was adjusted to around pH 9.0. The Final mixture was transferred to a 1000 ml volumetric flask and adjusted to 1000 ml volume by addition of water. Finally the pH of the solution was checked to remain at around pH 9.0.

Example 8

Manufacturing of a 1000 ml formulation with 17.5 mg nicotine/ml and pH 10.94.

To a beaker containing 950 ml water of room temperature was added 17.5 g nicotine (base) during stirring for about 5 minutes. The volume was adjusted to 1000 ml volume by addition of water. Finally the pH was checked.

Example 9

Manufacturing of a 1000 ml formulation with 17.5 mg nicotine/ml and pH 11.55.

To a beaker containing 950 ml water of room temperature was added 35 g sodium carbonate anhydrous during stirring until complete dissolution. Then 17.5 g nicotine (base) was added during stirring for about 5 minutes. The volume was adjusted to 1000 ml volume by addition of water. Finally the pH was checked.

Example 10

Manufacturing of a 1000 ml formulation with 15.65 mg nicotine/ml and pH 11.79.

To a beaker containing 950 ml water of room temperature was added 158 g glycine sodium salt during stirring until complete dissolution. Then 15.65 g nicotine (base) was added during stirring for about 5 minutes. The volume was adjusted to 1000 ml volume by addition of water. Finally the pH was checked.

Example 11

Buffer capacity determinations

Method: 10.0 ml of the respective below solutions was titrated with 0.1 M HCl to pH 7.0. The amount of 0.1 M HCl needed to decrease pH from 9.0 to 8.0 was determined.

Definitions: (1) Sodium hydrogen carbonate (NaHCO_3). Mw: 84.0
(2) Disodium phosphate dodecahydrate ($\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$) Mw: 358.1

Ingredient\Batch	DKN0293	DKN0294	DKN0295	DKN0296	DKN0290	DKN0291
Nicotine (mg/ml)			10.0		10.0	10.0
NaHCO ₃ (mg/ml)	16.8		16.8	8.4		
Na ₂ HPO ₄ ·12H ₂ O (mg/ml)		71.6		35.8	71.6	
Purified water ad	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml
Buffer Capacity PH=9.0-8.0 (mekv/l)	26.5	9.5	50	15.8	40	29

All solutions were adjusted to a pH of 9.0 when needed. A higher pH may cause irritation and corrosion, which might be harmful to the tissue of the oral cavity.

16.8 mg/ml of NaHCO₃ corresponds to 0.2 M.

71.6 mg/ml of Na₂HPO₄·12H₂O corresponds to 0.2 M.

5 8.4 mg/ml of NaHCO₃ corresponds to 0.1 M.

35.8 mg/ml of Na₂HPO₄·12H₂O corresponds to 0.1 M

Nicotine base has an alkalizing effect, but has too weak a buffering capacity on its own. The buffering capacity of the formulation is significantly and sufficiently increased when a buffering agent is added.

10 The above data clearly show that the present formulations have a good buffering capacity, providing for the desired rapid transmucousal uptake of nicotine.

A liquid pharmaceutical formulation according to the present invention may be administered using suitable devices being available on the market, e g spray devices.

15 Analysis of nicotine

The analysis of nicotine uptake and of the effect of the invention may be done according to standard procedures known in the art, e g using a bioanalysis for the determination of nicotine in the plasma of a subject.

Effects of the invention

20 Comparative tests were conducted as described above under Legend of figures.

Figure 1 shows that with a liquid pharmaceutical formulation according to the present invention the venous blood plasma level of nicotine ascends signify-

cantly more rapidly than with Nicorette Microtab[®]. Nicorette Microtab[®] has the same pharmacokinetic profile as, i e is pharmacologically equivalent with, Nicorette Gum[®] and all other nicotine chewing gums currently on the market. Nicotine chewing gums presently represent around half of the world sales of medicinal
5 nicotine-containing products for smoking cessation and similar indications.

Figure 2 shows that the higher the pH of a liquid pharmaceutical formulation according to the present invention the faster the absorption kinetics and the higher the plasma concentration of nicotine.

Figures 3 and 4 further show that a formulation according to the present
10 invention provides for a fast craving relief manifested through a significantly faster reduction in the urge to smoke compared to known oral nicotine formulations.

Use for therapy, treatment and manufacturing

The liquid pharmaceutical formulation product according to the invention may be used in therapy. Said therapy may be a treatment of a disease or medical
15 indication selected from the group consisting of reduction in use of tobacco, cessation of use of tobacco, other use of tobacco, temporary abstinence from abstaining from use of tobacco, Alzheimer's disease, Crohn's disease, Parkinson's disease, Tourette's syndrome, and ulcerative colitis; and weight control.

Nicotine in any form may be used for the manufacturing of a liquid pharma-
20 ceutical formulation according to the invention for the treatment of a disease or medical indication selected from the group consisting of reduction in use of tobacco, cessation of use of tobacco, other use of tobacco, temporary abstinence from abstaining from using tobacco, Alzheimer's disease, Crohn's disease, Parkinson's disease, Tourette's syndrome, and ulcerative colitis; and weight control.

CLAIMS

1. A liquid pharmaceutical formulation comprising nicotine in any form, characterized in that it is for administration to the oral cavity and that it is alkalized by buffering and/or pH regulation.
- 5 2. A liquid pharmaceutical formulation according to claim 1, characterized in that it is for administration to the oral cavity by spraying, dropping or pipetting, preferably by spraying, most preferably by spraying under the tongue.
3. A liquid pharmaceutical formulation according to any of claims 1 or 2, characterized in that it is alkalized by buffering and/or pH regulation in such
10 a way that upon administration to a subject the pH of the liquid of the oral cavity of the subject is transiently increased by about 0.3 to about 4 pH units.
4. A liquid pharmaceutical formulation according to claim 3, characterized in that it is alkalized by buffering and/or pH regulation in such a way that upon administration to a subject the pH of the liquid of the oral cavity of the subject
15 is transiently increased by about 0.5 to about 2.5 pH units.
5. A liquid pharmaceutical formulation according to any of claims 1 - 4, characterized in that it is alkalized by buffering and/or pH regulation by the use of one or more buffering agents selected from the group consisting of a carbonate, such as mono-carbonate, bicarbonate or sesquicarbonate; glycinate, phosphate,
20 glycerophosphate, acetate, gluconate or citrate of an alkali metal, such as potassium or sodium, or of ammonium, and mixtures thereof; and/or by the use of pH regulating agents, such as agents selected from the group consisting of sodium hydroxide, potassium hydroxide, calcium hydroxide and calcium oxide; and/or by using at least partly pH regulating forms of nicotine.
- 25 6. A liquid pharmaceutical formulation according to any of claims 1 - 5, wherein the nicotine in any form is selected from the group consisting of the free base form of nicotine, a nicotine salt, or a nicotine derivative; and mixtures thereof.
7. A liquid pharmaceutical formulation according to any of claims 1 - 5, wherein the nicotine in any form is selected from the group consisting of a nicotine
30 inclusion complex or nicotine in any non-covalent binding; and mixtures thereof.
8. A liquid pharmaceutical formulation according to claim 7, wherein the

nicotine inclusion complex is a cyclodextrin complex, such as a β -cyclodextrin complex.

9. A liquid pharmaceutical formulation according to claim 6, wherein the nicotine salt is a salt formed as tartrate, hydrogen tartrate, citrate or malate.

5 10. A liquid pharmaceutical formulation according to any of claims 1 - 9, wherein the amount of nicotine in any form delivered at each incidence of administration is about 0.05 - 10 mg calculated as the free base form of nicotine.

11. A liquid pharmaceutical formulation according to claim 10, wherein the amount of nicotine in any form delivered at each incidence of administration is
10 about 0.25 - 6 mg calculated as the free base form of nicotine.

12. A liquid pharmaceutical formulation according to claim 11, wherein the amount of nicotine in any form delivered at each incidence of administration is about 0.5 - 4 mg calculated as the free base form of nicotine.

13. A liquid pharmaceutical formulation according to any of claims 1 - 12,
15 wherein the liquid phase comprises water.

14. A liquid pharmaceutical formulation according to any of claims 1 - 12, wherein the liquid phase comprises an alcohol, such as ethanol, glycerol, propylene glycol and polyethylene glycol, or mixtures thereof.

15. A liquid pharmaceutical formulation according to any of claims 1 - 12,
20 wherein the liquid phase comprises one or more lipids.

16. A liquid pharmaceutical formulation according to any of claims 1 - 15, wherein the liquid phase comprises water and/or an alcohol, such as ethanol, glycerol, propylene glycol and polyethylene glycol, and/or one or more lipids or mixtures thereof.

25 17. A liquid pharmaceutical formulation according to any claims 1-16, characterized in that it further comprises one or more flavoring and/or aromatizing agents, such as those selected from the group consisting of essential oils obtained by distillations, solvent extractions or cold expressions of fresh or dried flowers, buds, leaves, stems, fruit, seeds, peel, bark, or root e g oil of pepper-
30 mint, spearmint, eucalyptus, wintergreen, niaouli, clove, cardamom, cinnamon, bitter almond, coriander, caraway, ginger, juniper, orange, bitter orange, lemon,

grapefruit, mandarine, bergamot, thyme, fennel and rosemary;

natural flavors and aroma agents including either diluted solutions of essential oils or concentrates of flavor components with natural origin from e g fruits, berries, nuts, spices, mints, tobacco, cocoa, coffee, tea, vanilla, liquorice,

5 caramel, toffee, honey, wine, liquors and brews;

synthetic flavors and aroma agents consisting of mixtures of chemicals comprising hydrocarbons, alcohols, aldehydes, esters, ketones, ethers and oxides blended to match the natural flavor of e g fruits, berries, nuts, spices, mints, tobacco, cocoa, coffee, tea, vanilla, liquorice, caramel, toffee, honey, wine, liquors

10 or brews;

and mixtures thereof.

18. A liquid pharmaceutical formulation according to any of claims 1 - 17, c h a r a c t e r i z e d in that it further comprises one or more stabilizing additives, such as those selected from the group consisting of antioxidants including vitamin

15 E, i e tocopheroles, vitamin C, i e ascorbic acid and its salts, sodium pyrosulfite, butylhydroxytoluene, butylated hydroxyanisole; and preservatives including parabenes, benzalkonium chloride, chlorbutanol, benzyl alcohol, beta-phenylethylal alcohol, cetylpyridinium chloride; and chelating agents, such as EDTA; and galates, such as propyl galate.

20 19. A liquid pharmaceutical formulation according to any of claims 1 - 18, c h a r a c t e r i z e d in that it further comprises one or more additives selected from the group consisting of:

thickening agents, such as natural, semisynthetic or synthetic polymers, e g starch and starch derivatives, cellulose and cellulose derivatives, polyethylene

25 glycols and derivatives thereof, polyacrylates, and polyvinyl esters and ethers;

enhancers, such as azone;

vitamins, such as vitamins C and E;

minerals, such as fluorides, especially sodium fluoride, sodium monofluoro phosphate and stannous fluoride;

30 anti-odours, such as zinc and cyclodextrins;

propellants, such as 1,1,2,2-tetrafluoroethane (HFC-134a), optionally being

liquefied, and 1,1,1,2,3,3,3-heptafluoropropane (HFC-227), optionally being liquefied;

sweeteners including one or more synthetic sweetening agents and/or natural sugars, such as those selected from the groups consisting of

5 artificial sweeteners e g saccharin and its sodium and calcium salts, aspartame, acesulfame and its potassium salt, thaumatin and glycyrrhizin;

polyhydric alcohols such as sorbitol, xylitol, mannitol and glycerol; monosaccharides including glucose (also called dextrose), fructose (also called laevulose) and galactose;

10 disaccharides including saccharose (also called sucrose), lactose (also called milk sugar) and maltose (also called malt sugar);

mixtures of sugars including liquid glucose syrup e g starch hydrolysates containing a mixture of chiefly dextrose, maltose, dextrans and water, invert sugar syrup e g sucrose inverted by invertase containing a mixture of dextrose, laevulose
15 and water, high sugar content syrups such as treacle, honey and malt extract; and mixtures thereof;

20. A liquid pharmaceutical formulation according to any of claims 1 - 19, characterized in that one or more of the compounds of the liquid pharmaceutical formulation is/are solubilized in one or more surface active agents and/or
20 emulsifiers, such as nonionic, cationic, anionic or zwitterionic surfactants, including amphiphilic block copolymers, or mixtures thereof.

21. A liquid pharmaceutical formulation according to claim 20, characterized in that one or more of the compounds of the liquid pharmaceutical formulation is/are solubilized in one or more surface active agents selected from

25 nonionic surface-active agents including poloxamers, e g

poly (oxypropylene)-poly(oxyethylene) block copolymers, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, mono- and diglycerides and esters thereof, polyoxyethylene stearates, polyglycerolesters of fatty acids (including polyglycerolpolyricinoleic acid
30 (PGPR)), and sorbitan fatty acid esters,

cationic surface-active agents including secondary, quaternary and tertiary

ammonium compounds and cationic phospholipids,

anionic surface-active agents including fatty acid salts, lactylates, especially sodium and/or calcium stearylactylate, alkyl sulphates, alkyl sulphonates, latanol, and anionic phospholipids, such as phosphatidylserine,

- 5 zwitterionic surface-active agents including zwitterionic phospholipids, such as phosphatidylcholine and phosphatidylethanolamine, or mixtures thereof, preferably surface-active agents or mixtures thereof being nonionic.

22. A liquid pharmaceutical formulation according to any of claims 1 - 21,
10 c h a r a c t e r i z e d in that it comprises nicotine base, sodium hydrogen carbonate acting as buffering agent, water acting as solvent, ethanol acting as co-solvent, a poloxamer acting as surface active agent, EDTA acting as chelating agent, Acesulfame K acting as sweetener, optionally one or more preservatives, and optionally one or more flavoring or aroma agents.

- 15 23. A method for delivering nicotine in any form to a subject comprising the steps of

a) administering to a subject a liquid pharmaceutical formulation according to any of claims 1- 22 into the oral cavity of the subject, and

- b) allowing the nicotine in any form in the liquid pharmaceutical
20 formulation to be systematically absorbed by the subject essentially by buccal uptake of nicotine.

24. A method according to claim 23, wherein absorption of said nicotine in any form results in a t_{\max} of nicotine in venous blood of the subject after about 3 - 30 minutes.

- 25 25. A method according to any of claims 23 - 24, wherein absorption of said nicotine in any form results in a t_{\max} of nicotine in venous blood of the subject after about 3 - 20 minutes.

26. A method according to any of claims 23 - 25, wherein absorption of said nicotine in any form results in a t_{\max} of nicotine in venous blood of the subject after
30 about 3 - 15 minutes.

27. A method for obtaining reduction of the urge to smoke or otherwise use

tobacco containing material and/or for providing a sense of smoking satisfaction without smoking, comprising the steps of

- a) replacing at least partly the tobacco containing material with a liquid pharmaceutical formulation according to any of claims 1 - 22,
 - 5 b) administering to a subject a liquid pharmaceutical formulation according to any of claims 1 - 22 into the oral cavity of the subject, and
 - c) allowing the nicotine in any form in the liquid pharmaceutical formulation to be systematically absorbed by the subject essentially by buccal uptake of nicotine.
- 10 28. A method according to claim 27, wherein absorption of said nicotine in any form results in a t_{\max} of nicotine in venous blood of the subject after about 3 - 30 minutes.
29. A method according to any of claims 27 - 28, wherein absorption of said nicotine in any form results in a t_{\max} of nicotine in venous blood of the subject after
15 about 3 - 20 minutes.
30. A method according to any of claims 27 - 29, wherein absorption of said nicotine in any form results in a t_{\max} of nicotine in venous blood of the subject after about 3 - 15 minutes.
31. A method according to any of claims 27 - 30, wherein the administering
20 to a subject of the liquid pharmaceutical formulation takes place by spraying, dropping or pipetting, preferably by spraying, most preferably by spraying under the tongue.
32. A method for obtaining reduction of the urge to smoke or otherwise use tobacco containing material and/or for providing a sense of smoking satisfaction
25 without smoking wherein a method according to claim 27 - 31 is used in combination with one or more other methods for obtaining reduction of the urge to smoke or otherwise use tobacco containing material and/or for providing a sense of smoking satisfaction without smoking.
33. A method according to claim 32, wherein the one or more other methods
30 is/are selected from the group consisting of administration through chewing gums, nasal sprays, transdermal patches, inhaling devices, lozenges, tablets and parenteral

means or methods, subcutaneous means or methods, intravenous means or methods, rectal means or methods, vaginal means or methods and transmucosal means or methods; or use of tobacco.

34. A method according to claim 33, wherein the one or more other methods
5 comprises administration of nicotine.

35. A system for delivering nicotine in any form to a subject, comprising a liquid pharmaceutical formulation according to any of claims 1 - 22 and at least one other means for delivering nicotine in any form to a subject.

36. A system for obtaining reduction of the urge to smoke or use of tobacco
10 and/or for providing a sense of smoking satisfaction without smoking, comprising a liquid pharmaceutical formulation according to any of claims 1 - 22 and at least one other means for obtaining reduction of the urge to smoke or use tobacco.

37. A system according to any of claims 35 - 36, wherein the at least one other means is/are selected from the group consisting of administration through
15 chewing gums, nasal sprays, transdermal patches, inhaling devices, lozenges, tablets and parenteral means or methods, subcutaneous means or methods, intravenous means or methods, rectal means or methods, vaginal means or methods and transmucosal means or methods; or use of tobacco.

38. A system according to claim 37, wherein the at least other means com-
20 prises administration of nicotine.

39. Use of a liquid pharmaceutical formulation according to any of claims 1 - 22 for obtaining a quick and/or complete reduction of the urge to smoke or use tobacco and/or for providing a sense of smoking satisfaction without smoking.

40. A use according to claim 39, wherein the reduction of the urge to smoke
25 or use tobacco is reduced by reaching a t_{\max} of nicotine in venous blood of the subject after about 3 - 30 minutes.

41. A use according to any of claims 39 and 40, wherein the reduction of the urge to smoke or use tobacco is reduced by reaching a t_{\max} of nicotine in venous blood of the subject after about 3 - 20 minutes.

30 42. A use according to any of claims 39 - 41, wherein the reduction of the urge to smoke or use of tobacco is reduced by reaching a t_{\max} of nicotine in venous

blood of the subject after about 3 - 15 minutes.

43. A use according to any of claims 39 - 42, wherein delivering of nicotine in any form results in a t_{\max} of nicotine in venous blood of the subject after about 3 - 30 minutes, preferably after about 3- 20 minutes, and most preferably after about 3 - 5 15 minutes.

44. A method for manufacturing a liquid pharmaceutical formulation according to any of claims 1 - 22, comprising the steps of:

- a) making a first mixture comprising a first solvent, at least one buffering agent and/or other means for pH regulation, and optionally nicotine in any form,
- 10 b) optionally adding first components to said first mixture, said first components optionally having been initially solubilized,
- c) optionally making one or more second mixture(s) comprising one or more second solvent(s) and second component(s), which may comprise nicotine in any form,
- 15 d) optionally mixing the first mixture and the optional one or more second mixture(s) to a final mixture, optionally under addition of one or more further solvent(s), and optionally under addition of nicotine in any form,
- e) optionally adjusting the pH of the final mixture.

45. A method according to claim 44, wherein the mixing is done in a temperature from about room temperature to about 95°C.

46. The method according to any of claims 44 - 45, wherein the nicotine in any form is selected from the group consisting of the free base form of nicotine, a nicotine salt, a nicotine derivative, such as a nicotine inclusion complex or nicotine in any non-covalent binding; and mixtures thereof.

47. The method according to any of claims 44 - 46, wherein the buffering and/or pH regulation is obtained by the use of one or more buffering agents selected from the group consisting of a carbonate, such as monocarbonate, bicarbonate or sesquicarbonate; glycinate, phosphate, glycerophosphate, acetate, gluconate or citrate of an alkali metal, such as potassium or sodium, or ammonium, and mixtures thereof; and/or by the use of pH regulating agents, such as agents selected from the group consisting of sodium hydroxide, potassium hydroxide, calcium hydroxide and 30

calcium oxide; and/or by using at least partly pH regulating forms of nicotine.

48. The method according to any of claims 44 - 47, wherein the first solvent and the optional one or more second solvent(s) is/are chosen from water and/or an alcohol, such as ethanol, glycerol, propylene glycol and polyethylene glycol, and/or
5 one or more lipids or mixtures thereof.

49. The method according to any of claims 44 - 48, wherein the optional first and second components are chosen from

one or more flavoring and/or aromatizing agents, such as those selected from the group consisting of essential oils obtained by distillations, solvent extractions or
10 cold expressions of fresh or dried flowers, buds, leaves, stems, fruit, seeds, peel, bark, or root e g oil of peppermint, spearmint, eucalyptus, wintergreen, niaouli, clove, cardamom, cinnamon, bitter almond, coriander, caraway, ginger, juniper, orange, bitter orange, lemon, grapefruit, mandarine, bergamot, thyme, fennel and rosemary;

15 natural flavors and aroma agents including either diluted solutions of essential oils or concentrates of flavor components with natural origin from e g fruits, berries, nuts, spices, mints, tobacco, cocoa, coffee, tea, vanilla, liquorice, caramel, toffee, honey, wine, liquors and brews;

synthetic flavors and aroma agents consisting of mixtures of chemicals
20 comprising hydrocarbons, alcohols, aldehydes, esters, ketones, ethers and oxides blended to match the natural flavor of e g fruits, berries, nuts, spices, mints, tobacco, cocoa, coffee, tea, vanilla, liquorice, caramel, toffee, honey, wine, liquors or brews;

and mixtures thereof;

25 one or more stabilizing additives, such as those selected from the group consisting of antioxidants including vitamin E, i e tocopheroles, vitamin C, i e ascorbic acid and its salts, sodium pyrosulfite, butylhydroxytoluene, butylated hydroxyanisole; and preservatives including parabenes, benzalkonium chloride, chlorbutanol, benzyl alcohol, beta-phenylethylal alcohol, cetylpyridinium chloride;
30 and chelating agents, such as EDTA; and galates, such as propyl galate;

one or more additives selected from the group consisting of

- thickening agents, such as natural, semisynthetic or synthetic polymers, e g starch and starch derivatives, cellulose and cellulose derivatives, polyethylene glycols and derivatives thereof, polyacrylates, and polyvinyl esters and ethers; enhancers, such as azone;
- 5 vitamins, such as vitamins C and E;
- minerals, such as fluorides, especially sodium fluoride, sodium monofluorophosphate and stannous fluoride;
- anti-odours, such as zinc and cyclodextrins;
- propellants, such as 1,1,2,2-tetrafluoroethane (HFC-134a), optionally being
- 10 liquefied, and 1,1,1,2,3,3,3-heptafluoropropane (HFC-227), optionally being liquefied;
- sweeteners including one or more synthetic sweetening agents and/or natural sugars, such as those selected from the groups consisting of
- artificial sweeteners e g saccharin and its sodium and calcium salts, aspar-
- 15 tame, acesulfame and its potassium salt, thaumatin and glycyrrhizin;
- polyhydric alcohols such as sorbitol, xylitol, mannitol and glycerol; monosaccharides including glucose (also called dextrose), fructose (also called laevulose) and galactose;
- disaccharides including saccharose (also called sucrose), lactose (also called
- 20 milk sugar) and maltose (also called malt sugar);
- mixtures of sugars including liquid glucose syrup e g starch hydrolysates containing a mixture of chiefly dextrose, maltose, dextrans and water, invert sugar syrup e g sucrose inverted by invertase containing a mixture of dextrose, laevulose and water, high sugar content syrups such as treacle, honey and malt extract;
- 25 and mixtures thereof.
50. The method according to any of claims 44 - 49, wherein the first and/or second components is/are solubilized in one or more surface active agents and/or emulsifiers, such as nonionic, cationic, anionic or zwitterionic surfactants, including amphiphilic block copolymers, or mixtures thereof, whereby preferably the one or
- 30 more surface active agents is/are selected from

nonionic surface-active agents including poloxamers, e g
poly(oxypropylene)-poly(oxyethylene) block copolymers, polyoxyethylene alkyl
ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid
esters, mono- and diglycerides and esters thereof, polyoxyethylene stearates, poly-
5 glycerolesters of fatty acids (including polyglycerolpolyricinoleic acid (PGPR)),
and sorbitan fatty acid esters,

cationic surface-active agents including secondary, quaternary and tertiary
ammonium compounds and cationic phospholipids,

anionic surface-active agents including fatty acid salts, lactylates, especially
10 sodium and/or calcium stearylactylate, alkyl sulphates, alkyl sulphonates, latanol,
and anionic phospholipids, such as phosphatidylserine,

zwitterionic surface-active agents including zwitterionic phospholipids, such
as phosphatidylcholine and phosphatidylethanolamine,

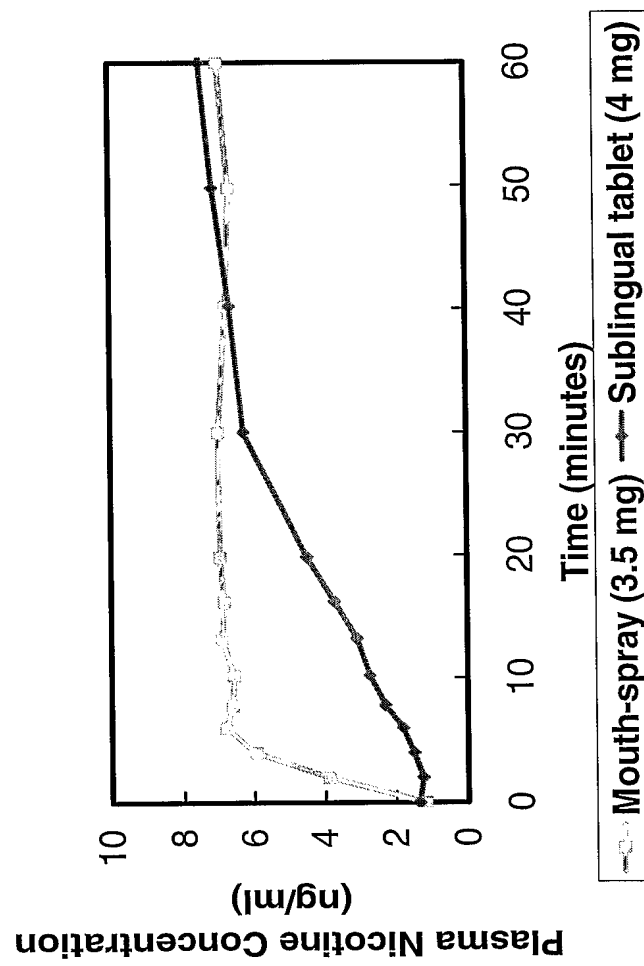
or mixtures thereof, whereby most preferably the surface-active agents or
15 mixtures thereof are nonionic.

51. A liquid pharmaceutical formulation according to any of claims 1 - 22
for use in therapy.

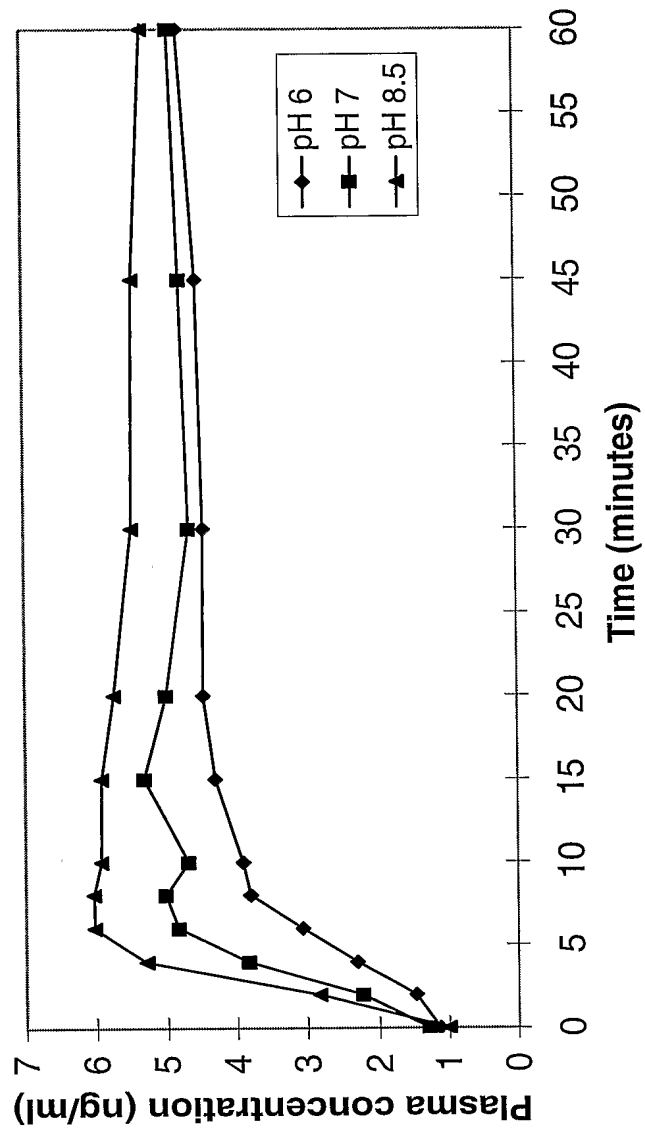
52. A liquid pharmaceutical formulation according to claim 51, wherein the
therapy is treatment of a disease selected from the group consisting of addiction to
20 tobacco or nicotine, Alzheimer's disease, Crohn's disease, Parkinson's disease,
Tourette's syndrome, ulcerative colitis; and weight control.

53. Use of nicotine in any form for the manufacturing of a liquid pharma-
ceutical formulation according to any of claims 1 - 22 for the treatment of a disease
selected from the group consisting of addiction to tobacco or nicotine, Alzheimer's
25 disease, Crohn's disease, Parkinson's disease, Tourette's syndrome, ulcerative
colitis; and weight control.

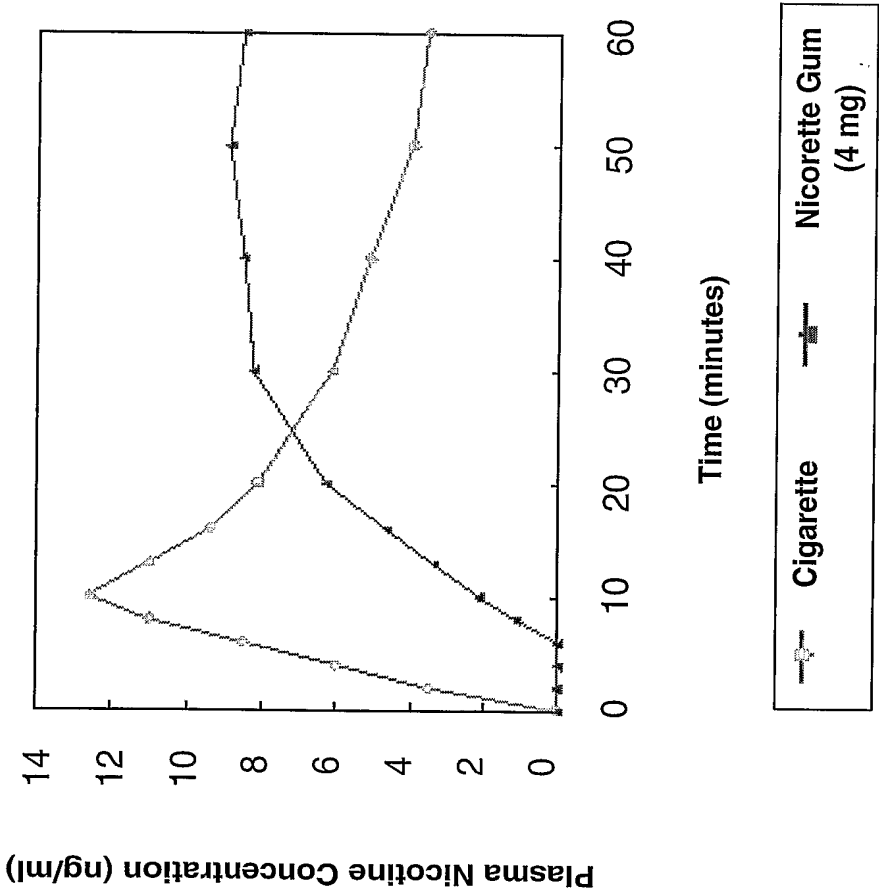
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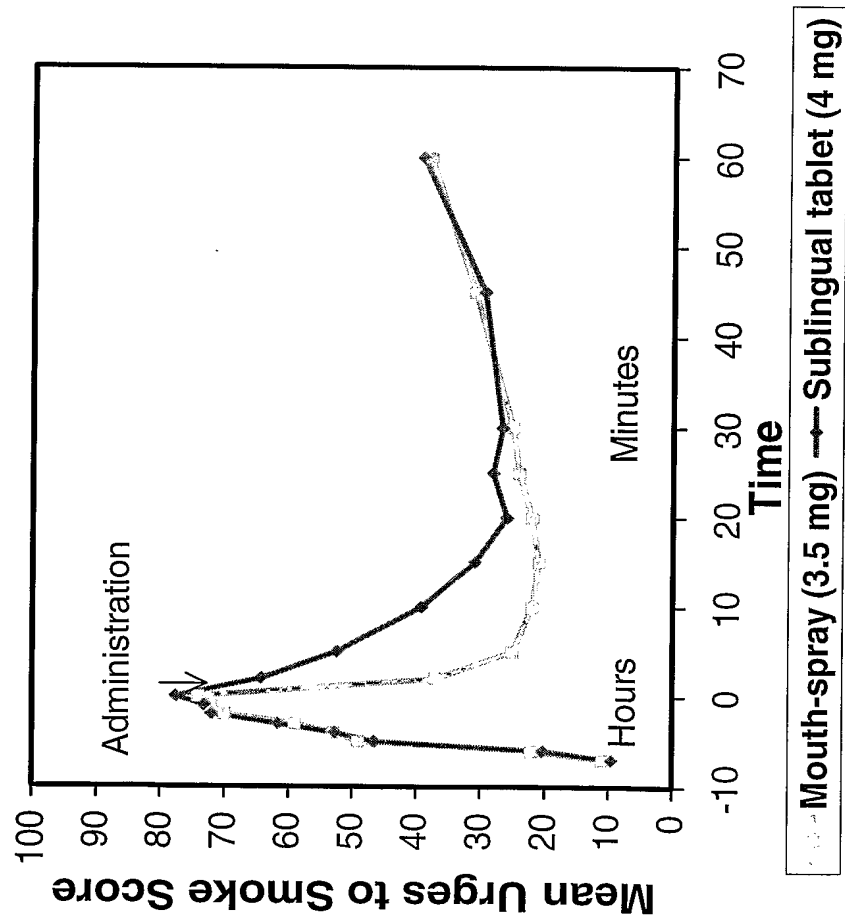
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/02358

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/465, A61P 25/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, CHEM. ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5721257 A (RICHARD W. BAKER ET AL), 24 February 1998 (24.02.98), see column 15, lines 45-67, column 16, lines 1-44 and example 33	1,3-53
Y	--	2
Y	US 5955098 A (HARRY A. DUGGER, III), 21 Sept 1999 (21.09.99), see the claims and example	2
A	Eur J Clin Pharmacol, Volume 56, 2001, L. Molander et al: "Pharmacokinetic investigation of a nicotine sublingual tablet", page 813 - page 819	1-53
	--	

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

3 April 2003

04-04-2003

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/02358

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Expert Opin. Pharmacother., Volume 2, no. 10, 2001, Bridgette E Garrett et al: "Tobacco addiction and pharmacological interventions", page 1545 - page 1555 -- -----	1-53

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/SE02/02358**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **23-34**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/02358

Claims 23-34 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/02/03

International application No.

PCT/SE 02/02358

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
US	5721257	A	24/02/98	US	5362496	A	08/11/94
				US	5593684	A	14/01/97
US	5955098	A	21/09/99	AU	2190797	A	07/11/97
				CA	2252050	A	23/10/97
				EP	0904055	A	31/03/99
				EP	1275374	A	15/01/03
				WO	9738663	A	23/10/97